

IAP11 Rec'd PCT/PTO 15 AUG 2006

IMIDAZOLINE DERIVATIVES HAVING CB₁-ANTAGONISTIC ACTIVITY

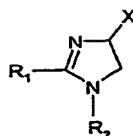
The present invention relates to 1,2,4-tri-substituted imidazoline derivatives as CB₁ antagonists, to methods for the preparation of these compounds and to novel intermediates useful for the synthesis of said imidazoline derivatives. The invention also relates to the use of a compound disclosed herein for the manufacture of a medicament giving a beneficial effect. A beneficial effect is disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. The invention also relates to the use of a compound of the invention for the manufacture of a medicament for treating or preventing a disease or condition. More particularly, the invention relates to a new use for the treatment of a disease or condition disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. In embodiments of the invention specific compounds disclosed herein are used for the manufacture of a medicament useful in the treatment of disorders in which cannabinoid receptors are involved, or that can be treated via manipulation of those receptors.

Multisubstituted imidazoline derivatives are known from WO 03/101954 and WO 03/101969. The compounds described therein, are potent inhibitors of transcription factor NF- κ B, making them useful in the treatment of certain types of tumors. Said imidazoline derivatives also have potent activities as anti-inflammatory agents and antibiotics, leading to an additional array of indications in which they are likely to be of therapeutic interest, including inflammatory and infectious diseases. The compounds described in the abovementioned patent applications were not demonstrated to have any affinity for cannabinoid receptors, and therefore unlikely to be of therapeutic value in disorders in which these cannabinoid receptors are involved.

The goal of the present invention was to identify imidazoline derivatives with potent activity as cannabinoid-CB₁ receptor modulators, whilst maintaining essentially the physico-chemical properties that make some imidazoline derivatives useful therapeutic agents.

It has now surprisingly been found that potent antagonism or inverse agonism of cannabinoid-CB₁ receptors is present in the novel 4,5-dihydro-1H-imidazole derivatives of the formula (I):

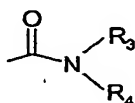
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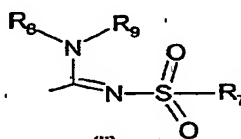
(I)

wherein:

- 5 — R_1 and R_2 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3} -alkyl or C_{1-3} -alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphthyl,
- 10 — X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein:

- 15 — R_3 represents a hydrogen atom or a branched or linear C_{1-3} alkyl group,
- R_4 represents a branched or linear C_{1-8} alkyl or C_{3-8} -cycloalkyl- C_{1-2} -alkyl group, branched or linear C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenyl, phenoxy, benzyl, phenethyl or phenylpropyl group, optionally substituted on their phenyl ring with 1-3 substituents Y, wherein Y has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein R_5 and R_6 - together with the nitrogen atom to which they are attached - form a
- 20 saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom, or
- 25

5 R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, amino, hydroxy or trifluoromethyl group or a fluoro atom,

– R_7 represents a benzyl, phenyl, thienyl or pyridyl group, which groups may be substituted on their aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_7 represents naphthyl or R_7 represents an amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom,

– R_8 represents a hydrogen atom or a methyl group,
20 – R_9 represents a hydrogen atom or a methyl, ethyl or methoxy group

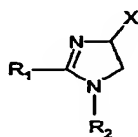
and tautomers, stereoisomers, prodrugs and salts thereof.

25 At least one centre of chirality is present (at the C_4 position of the imidazoline moiety) in the compounds of the formula (I). The invention relates to racemates, mixtures of diastereomers as well as the individual stereoisomers of the compounds having formula (I). The invention also relates to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

30 Prodrugs of the compounds mentioned above are in the scope of the present invention. Prodrugs are therapeutic agents which are inactive per se but are transformed into one or more active metabolites. Prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility,
35 permeability, stability, presystemic metabolism and targeting limitations (Medicinal Chemistry: Principles and Practice, 1994, ISBN 0-85186-494-5, Ed.: F. D. King, p. 215; J. Stella, "Prodrugs as therapeutics", Expert Opin. Ther. Patents, 14(3), 277-

280, 2004; P. Ettmayer et al., "Lessons learned from marketed and investigational prodrugs", J.Med.Chem., 47, 2393-2404, 2004). Pro-drugs, i.e. compounds which when administered to humans by any known route, are metabolised to compounds having formula (1), belong to the invention. In particular this relates to compounds with primary or secondary amino or hydroxy groups. Such compounds can be reacted with organic acids to yield compounds having formula (1) wherein an additional group is present which is easily removed after administration, for instance, but not limited to amidine, enamine, a Mannich base, a hydroxyl-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate, ester, amide or enaminone.

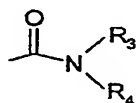
The invention particularly relates to compounds having formula (I)



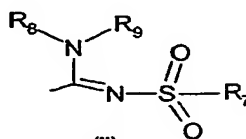
(I)

wherein:

- R_1 and R_2 independently represent phenyl, which phenyl group may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3} -alkyl or C_{1-3} -alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphthyl, thienyl or pyridyl,
- X represents one of the subgroups (i) or (ii).



(i)



(ii)

wherein:

- R_3 represents a hydrogen atom,

- R₄ represents a branched or linear C₁₋₈ alkyl, branched or linear C₁₋₈ alkoxy or C₃₋₈ cycloalkyl group, which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R₄ represents a phenyl, phenoxy, pyridyl or thienyl group, or R₄ represents a group NR₅R₆ wherein
 - 5 R₅ and R₆ - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) or
 - 10 R₃ and R₄ - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a methyl, hydroxy or trifluoromethyl group or a fluoro atom,
 - R₇ represents a phenyl group, which phenyl group may be substituted on its aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R₇ represents C₁₋₈
 - 15 branched or linear alkyl, C₃₋₁₀ cycloalkyl or C₅₋₁₀ bicycloalkyl, or R₇ represents naphthyl or R₇ represents an amino group or R₇ represents a C₁₋₈ dialkylamino group, a C₁₋₈ monoalkylamino group or a saturated or unsaturated, monocyclic or
 - 20 bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C₁₋₃ alkyl or hydroxy group,
 - R₈ represents a hydrogen atom,
 - 25 - R₉ represents a hydrogen atom

and tautomers, stereoisomers, prodrugs and salts thereof.

- Due to the potent CB₁ antagonistic activity the compounds according to the invention
 - 30 are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, in particular juvenile obesity and drug induced obesity, addiction, impulse control disorders, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle
 - 35 spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke,

spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, 5 diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, cardiovascular disorders, atherosclerosis, liver cirrhosis and sexual disorders.

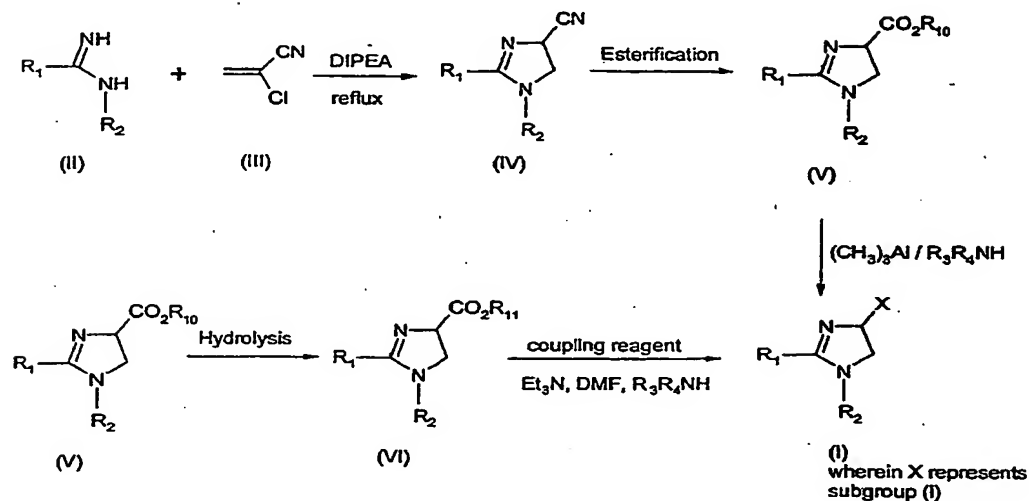
The cannabinoid receptor modulating activity of the compounds of the invention makes them particularly useful in the treatment of obesity, juvenile obesity 10 and drug induced obesity, when used in combination with lipase inhibitors. Specific examples of compounds which can be used in such combination preparations are (but not restricted to) the synthetic lipase inhibitor orlistat, lipase inhibitors isolated from micro organisms such as lipstatin (from *Streptomyces toxytricini*), ebelactone B (from *Streptomyces aburaviensis*), synthetic derivatives of these compounds, as well 15 as extracts of plants known to possess lipase inhibitory activity, for instance extracts of *Alpinia officinarum* or compounds isolated from such extracts like 3-methylethergalangin (from *A. officinarum*).

GENERAL ASPECTS OF SYNTHESSES

- The synthesis of compounds having formula (I) wherein X represents subgroup (i) is outlined in Scheme 1. Intermediates having general formula (II) can be obtained according to methods known, see for example: I. K. Khanna et al., J. Med. Chem. 2000, 43, 3168-3185; I. K. Khanna et al., J. Med. Chem. 1997, 40, 1634-1647; WO 03/027076 or WO 03/040107. Intermediates having general formula (IV) can be obtained according to methods known, see for example: I. K. Khanna et al., J. Med. Chem. 2000, 43, 3168-3185.
- 5 Carboxamidine derivatives of general formula (II) can be reacted with 2-chloroacrylonitrile (III) to give a 4,5-dihydro-1H-imidazole derivative of general formula (IV). This reaction is preferably carried out in the presence of a base such as N,N-diisopropylethylamine. The obtained derivatives of general formula (IV) can be esterified with an alcohol R_{10} -OH to give a 4,5-dihydro-1H-imidazole derivative of general formula (V), wherein R_{10} represents a branched or linear C_{1-5} alkyl group or a benzyl group. This reaction is preferably carried out under acidic conditions. A compound of general formula (V) can react with an amine R_3R_4NH , preferably in the presence of trimethylaluminum (Me_3Al) to give a compound of formula (I), wherein X represents subgroup (i) and R_3 and R_4 have the meaning as given above on page 2.
- 10 Additional information on trimethylaluminum $Al(CH_3)_3$ promoted amidation reactions of esters can be found in: J. I. Levin, E. Turos, S. M. Weinreb, *Synth Commun.* (1982), 12, 989-993.
- Alternatively, a compound of general formula (V) can be hydrolysed to the corresponding carboxylic acid derivative of general formula (VI), wherein R_{11} represents H or an earth alkali metal, in particular Li, Na or K. Alternatively, the compound of general formula (VI) can be reacted with a chlorinating agent such as thionylchloride to give the corresponding acid chloride. The compound of general formula (VI) can be reacted with an amine R_3R_4NH to give a compound of formula (I), wherein X represents subgroup (i) and R_3 and R_4 have the meaning as given above on page 2, via activating and coupling methods such as formation of an active ester, or in the presence of a so-called coupling reagent, such as for example, DCC, HBTU, BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) and the like. Additional information on activating and coupling methods of amines to carboxylic acids can be found in:
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- a) M. Bodanszky and A. Bodanszky: *The Practice of Peptide Synthesis*, Springer-Verlag, New York, 1994; ISBN: 0-387-57505-7;
 b) K. Akaji *et al.*, *Tetrahedron Lett.* (1994), 35, 3315-3318);
 c) F. Albericio *et al.*, *Tetrahedron Lett.* (1997), 38, 4853-4856).

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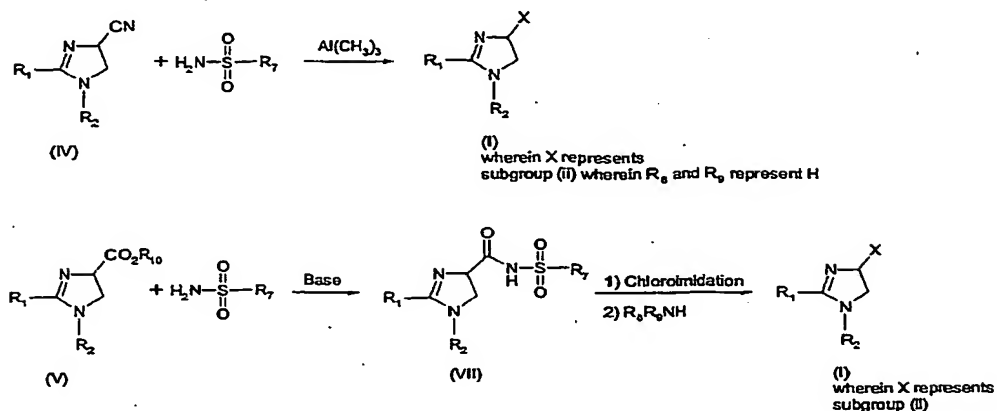
Scheme 1

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The synthesis of compounds having formula (I) wherein X represents subgroup (ii) is outlined in Scheme 2.

- An intermediate of general formula $R_7SO_2NH_2$ is either commercially available or can be prepared via standard synthetic methodology, for example from the corresponding compound R_7SO_2Cl (see for example; McManus *et al.*, *J. Med. Chem.* 1965, 8, 766). A compound of general formula (IV) can be reacted with a compound of general formula $R_7SO_2NH_2$ in the presence of a Lewis acid such as for example $AlMe_3$ in an inert organic solvent such as benzene to give a compound of general formula (I) wherein X represents subgroup (ii) and R_1 , R_2 and R_7 have the meaning as given above on the pages 1-3 and wherein R_8 and R_9 represent a hydrogen atom. A compound of general formula (V) may be reacted with a compound of general formula $R_7SO_2NH_2$ to give a compound of general formula (VII). This reaction is preferably carried out in the presence of a strong non-nucleophilic base. A compound of general formula (VII) may be reacted with a chlorinating reagent in a

chloroimidation reaction and subsequently treated with an amine R_8R_9NH to give a compound of formula (I), wherein X represents subgroup (ii).



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Scheme 2

The selection of the particular synthetic method depends on factors such as the compatibility of functional groups with the reagents used, the possibility to use protecting groups, catalysts, activating and coupling reagents and the ultimate structural features present in the final compound being prepared.

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According to these procedures the following compounds can be prepared. They are intended to further illustrate the invention in more detail, and therefore are not deemed to restrict the scope of the invention in any way.

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PHARMACEUTICAL PREPARATIONS

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxillary substances such as liquid or solid carrier material. The pharmaceutical compositions of the invention may be administered enterally, orally, parenterally (intramuscularly or intravenously), rectally or locally (topically). They can be administered in the form of solutions, powders, tablets, capsules (including microcapsules), ointments (creams or gel) or suppositories. Suitable excipients for such formulations are the pharmaceutically customary liquid or solid fillers and extenders, solvents, emulsifiers, lubricants, flavorings, colorings and/or buffer substances. Frequently used auxillary substances which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

Compounds of the present invention are generally administered as pharmaceutical compositions which are important and novel embodiments of the invention because of the presence of the compounds, more particularly specific compounds disclosed herein. Types of pharmaceutical compositions that may be used include but are not limited to tablets, chewable tablets, capsules, solutions, parenteral solutions, suppositories, suspensions, and other types disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. In embodiments of the invention, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more of the ingredients of a pharmaceutical composition of the invention. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration.

PHARMACOLOGICAL METHODS

In vitro affinity for cannabinoid-CB₁ receptors

- 5 The affinity of the compounds of the invention for cannabinoid CB₁ receptors can be determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB₁ receptor is stably transfected in conjunction with [³H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [³H]-ligand, with or without addition of compounds of the
10 invention, separation of bound and free ligand is performed by filtration over glassfiber filters. Radioactivity on the filter is measured by liquid scintillation counting.

In vitro cannabinoid-CB₁ receptor antagonism

- 15 *In vitro* CB₁ receptor antagonism can be assessed with the human CB₁ receptor cloned in Chinese hamster ovary (CHO) cells. CHO cells are grown in a Dulbecco's Modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum. Medium is aspirated and replaced by DMEM, without fetal calf serum, but containing [³H]-arachidonic acid and incubated overnight in a cell
20 culture stove (5% CO₂/95% air; 37 °C; water-saturated atmosphere). During this period [³H]-arachidonic acid is incorporated in membrane phospholipids. On the test day, medium is aspirated and cells are washed three times using 0.5 mL DMEM, containing 0.2% bovine serum albumin (BSA). Stimulation of the CB₁ receptor by WIN 55,212-2 leads to activation of PLA₂ followed by release of [³H]-arachidonic acid
25 into the medium. This WIN 55,212-2-induced release is concentration-dependently antagonized by CB₁ receptor antagonists.

In vivo cannabinoid-CB₁ receptor antagonism

- 30 *In vivo* CB₁ antagonism can be assessed with the CP-55,940-induced hypotension test in rat. Male normotensive rats (225-300 g; Harlan, Horst, The Netherlands) are anaesthetized with pentobarbital (80 mg/kg *i.p.*). Blood pressure is measured, via a cannula inserted into the left carotid artery, by means of a Spectramed DTX-plus pressure transducer (Spectramed B.V., Bilthoven, The Netherlands). After
35 amplification by a Nihon Kohden Carrier Amplifier (Type AP-621G; Nihon Kohden B.V., Amsterdam, The Netherlands), the blood pressure signal is registered on a

personal computer (Compaq Deskpro 386s), by means of a Po-Ne-Mah data-acquisition program (Po-Ne-Mah Inc., Storrs, USA). Heart rate is derived from the pulsatile pressure signal. All compounds are administered orally as a microsuspension in 1% methylcellulose 30 minutes before induction of the anesthesia which is 60 minutes prior to administration of the CB₁ receptor agonist CP-55,940. The injection volume is 10 ml/kg. After haemodynamic stabilization the CB₁ receptor agonist CP-55,940 (0.1 mg/kg *i.v.*) is administered and the hypotensive effect established. (Wagner, J. A.; Jarai, Z.; Batkai, S.; Kunos, G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB₁ receptors. *Eur.J.Pharmacol.* 2001, 423, 203-10).

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid, for instance an inorganic acid such as hydrochloric acid, or with an organic acid.

DOSE

The affinity of the compounds of the invention for cannabinoid receptors was determined as described above. From the binding affinity measured for a given compound of formula (1), one can estimate a theoretical lowest effective dose. At a concentration of the compound equal to twice the measured K_d-value, 100% of the cannabinoid receptors likely will be occupied by the compound. Converting that concentration to mg of compound per kg of patient yields a theoretical lowest effective dose, assuming ideal bioavailability. Pharmacokinetic, pharmacodynamic, and other considerations may alter the dose actually administered to a higher or lower value. The dosage expediently administered is 0.001 – 1000 mg/kg, preferably 0.1-100 mg/kg of patient's bodyweight.

EXAMPLE 1: SYNTHESSES OF SPECIFIC COMPOUNDS**Compounds 1 - 2**

- 5 **Part A:** A magnetically stirred mixture of N-(4-chlorophenyl)-2,4-dichlorobenzenecarboxamidine (10.0 gram, 0.033 mol), 2-chloroacrylonitrile (5.7 gram, 0.065 mol) and N,N-diisopropylethylamine (DIPEA) (12.5 ml, 0.069 mol) in tetrahydrofuran (150 ml) is heated at reflux temperature for 40 hours (N₂ atmosphere). After cooling to room temperature the mixture is concentrated in vacuo.
- 10 The residue is dissolved in a mixture of dichloromethane and water (200 ml/200 ml). The dichloromethane layer is collected, dried over MgSO₄, filtered and concentrated in vacuo. The residue is recrystallised from ethanol/water to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (11.23 gram, 97 % yield). ¹H-NMR (400 MHz, CDCl₃): δ 4.28 (dd, J = 10 and 8 Hz, 1H), 4.36 (t, J = 10
- 15 Hz, 1H), 5.07 (dd, J = 10 and 8 Hz, 1H), 6.68 (br d, J = 8 Hz, 2H), 7.16 (br d, J = 8 Hz, 2H), 7.32-7.36 (m, 2H), 7.45 (d, J = 8 Hz, 1H).

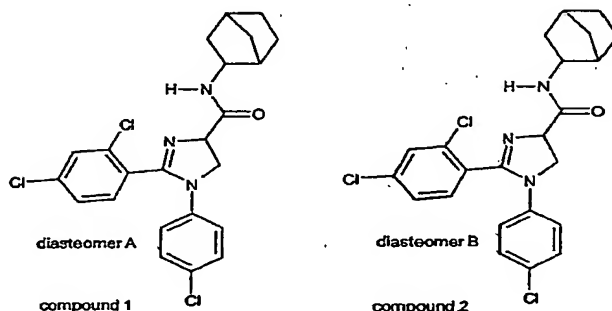
- Part B:** Acetyl chloride (17.76 ml, 0.25 mol) is slowly added to ethanol (1 l) to give solution A. 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (17.52 gram, 0.05 mol) is added in one portion to solution A. After cooling
- 20 to room temperature the mixture is stirred for another 40 hours and concentrated in vacuo. The residue is dissolved in dichloromethane and washed (3x) with aqueous (5 %) NaHCO₃. The dichloromethane layer is separated, dried over MgSO₄, filtered and concentrated in vacuo to give ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-
- 25 dihydro-1H-imidazole-4-carboxylate (18.0 gram, 90 % yield) as a brown oil that slowly solidifies on standing. ¹H-NMR (400 MHz, CDCl₃): δ 1.34 (t, J = 7 Hz, 3H), 4.15 (dd, J = 10 and 8 Hz, 1H), 4.22-4.41 (m, 3H), 4.91 (dd, J = 10 and 8 Hz, 1H), 6.66 (br d, J = 8 Hz, 2H), 7.11 (br d, J = 8 Hz, 2H), 7.30 (dd, J = 8 and 2 Hz, 1H), 7.33 (d, J = 2 Hz, 1H), 7.46 (dd, J = 8 Hz, 1H).

- 30 **Part C:** To a magnetically stirred solution of exo-2-aminobicyclo[2.2.1]heptane (0.67 ml, 0.009 mol) in anhydrous dichloromethane (10 ml) is added trimethylaluminum (5.4 ml of a 2N solution in hexane, 0.0108 mol) and the resulting solution is stirred for 20 minutes at room temperature. A solution of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (2.385 g, 0.006 mol) in
- 35 anhydrous dichloromethane (10 ml) is slowly added and the resulting mixture is

reacted at 40 °C for 40 hours (N₂ atmosphere). After cooling to room temperature the mixture is quenched with aqueous (5 %) NaHCO₃ and extracted with dichloromethane. The dichloromethane layer is separated, dried over MgSO₄, filtered and concentrated in vacuo to give a crude yellow syrup (2.58 gram) which is further purified with flash chromatography (silica gel, ethyl acetate/petroleum ether = 8/2 (v/v)) to give the faster moving 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (dia-stereomer A) (0.70 gram, 25 % yield) and the slower moving 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (diastereomer B) (0.69 gram, 25 % yield).

Diastereomer A: ¹H-NMR (400 MHz, CDCl₃): δ 1.10-1.58 (m, 7H), 1.76-1.84 (m, 1H), 2.26-2.30 (m, 2H), 3.74-3.82 (m, 1H), 4.27 (d, J ~ 10 Hz, 2H), 4.78 (t, J ~ 10 Hz, 1H), 6.65 (br d, J = 8 Hz, 2H), 6.70-6.78 (m, 1H), 7.12 (br d, J = 8 Hz, 2H), 7.29 (br s, 2H), 7.40 (br s, 1H).

Diastereomer B: ¹H-NMR (400 MHz, CDCl₃): δ 1.10-1.56 (m, 7H), 1.78-1.85 (m, 1H), 2.17-2.20 (m, 1H), 2.26-2.30 (m, 1H), 3.76-3.82 (m, 1H), 4.25-4.30 (m, 2H), 4.78 (dd, J = 10 and 8 Hz, 1H), 6.66 (br d, J = 8 Hz, 2H), 6.80 (br d, J ~ 7 Hz, 1H), 7.11 (br d, J = 8 Hz, 2H), 7.30 (br s, 2H), 7.41 (br s, 1H).

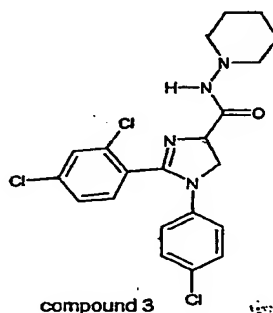


Compounds 3 and 4

Part A: A mixture of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3.97 g, 0.01 mol) in methanol/water is reacted with LiOH (1.3 gram, 0.054 mol) at room temperature for 16 hours. The resulting mixture is

concentrated in vacuo to give crude lithium 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (4.7 gram).

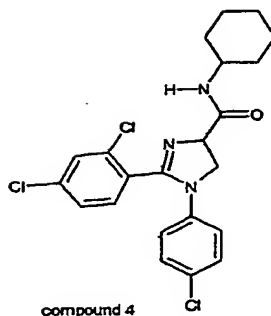
Part B: A mixture of the crude lithium 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (1.0 gram, ~ 0.0027 mol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (1.2 gram, 0.0027 mol), 1-aminopiperidine (0.3 gram, 0.003 mol) and triethylamine (1 ml) in DMF (30 ml) is stirred at room temperature for 16 hours. After concentration in vacuo, water is added and the resulting mixture is extracted (2x) with dichloromethane. The dichloromethane layers are collected, dried over MgSO_4 , filtered and concentrated in vacuo to give a residue that is further purified by flash chromatography (silicagel, dichloromethane/methanol = 95/5 (v/v)) to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-4,5-dihydro-1H-imidazole-4-carboxamide (380 mg, 31 % yield). Melting point: 113-116 °C. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 1.33-1.48 (m, 2H), 1.60-1.80 (m, 4H), 2.68-2.82 (m, 4H), 4.28-4.35 (m, 2H), 4.84 (dd, $J = 11$ and 9 Hz, 1H), 6.65 (br d, $J = 8$ Hz, 2H), 7.11 (br d, $J = 8$ Hz, 2H), 7.23-7.33 (m, 2H), 7.41 (d, $J = 2$ Hz, 1H), 7.57 (br s, 1H).



In an analogous manner compound 4 was prepared:

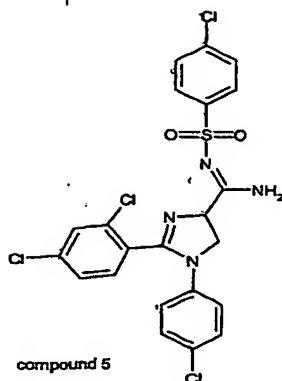
Compound 4: 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-cyclohexyl-4,5-dihydro-1H-imidazole-4-carboxamide. Melting point: 127-129 °C. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 1.04-2.03 (m, 10H), 3.73-3.92 (m, 1H), 4.23-4.33 (m, 2H), 4.81 (t, $J \sim 10$ Hz, 1H), 6.66 (br d, $J = 8$ Hz, 2H), 6.79 (br d, $J \sim 7$ Hz, 1H), 7.12 (br d, $J = 8$ Hz, 2H), 7.25-7.32 (m, 2H), 7.41 (br s, 1H).

16

**Compounds 5 – 8**

- Part A:** To a suspension of 4-chlorobenzenesulfonamide (0.45 gram, 0.00236 mol) in benzene (5 ml) is dropwise added trimethylaluminum (1.2 ml of a 2N solution in toluene, 0.0024 mol) to give a clear solution which is stirred at room temperature for 1 hour. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (0.55 gram, 0.00157 mol) is added and the resulting mixture is heated at 90 °C for 16 hours. After cooling to room temperature a mixture of methanol/water (8/2 (v/v)) is slowly added, the solids are removed by filtration and washed with chloroform (50 ml). The filtrate is concentrated in vacuo. The residue is triturated with n-pentane and twice recrystallised from methanol to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamidine (0.435 gram, 51 % yield). Melting point: 165-166 °C. ¹H-NMR (200 MHz, CDCl₃): δ 4.11-4.35 (m, 2H), 4.94 (dd, J = 12 and 10 Hz, 1H), 6.63 (br d, J = 8 Hz, 2H), 7.12 (br d, J = 8 Hz, 2H), 7.22-7.52 (m, 6H), 7.90 (br d, J = 8 Hz, 2H), 8.10-8.20 (m, 1H).

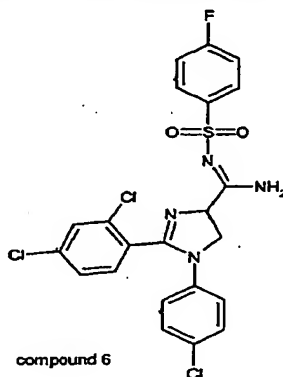
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In an analogous manner the compounds having formula (I) listed below have been prepared:

5

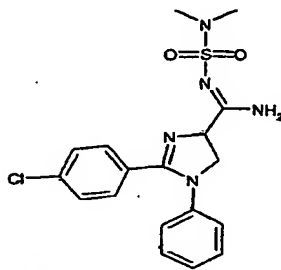
Compound 6: 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-fluorophenyl)sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamide. Melting point: 172-175 °C. ^1H -NMR (200 MHz, CDCl_3): δ 4.12-4.35 (m, 2H), 4.93 (dd, $J = 12$ and 10 Hz, 1H), 6.63 (br d, $J = 8$ Hz, 2H), 7.08-7.43 (m, 8H), 7.90-8.02 (m, 2H), 8.10-8.20 (m, 1H).



10

Compound 7: 2-(4-Chlorophenyl)-N-(dimethylaminosulfonyl)-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxamide. Melting point: 136-139 °C. ¹H-NMR (200 MHz, CDCl₃): δ 2.79 (s, 6H), 4.20-4.40 (m, 2H), 4.97 (t, J = 10 Hz, 1H), 6.83 (br d, J = 8 Hz, 2H), 7.05-7.50 (m, 8H), 7.80-7.90 (m, 1H).

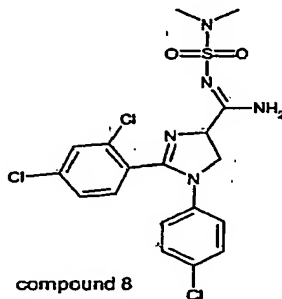
5



compound 7

Compound 8: 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(dimethylaminosulfonyl)-4,5-dihydro-1H-imidazole-4-carboxamide. Melting point: 146-147 °C.

10



compound 8

EXAMPLE 2: FORMULATIONS AS USED IN ANIMAL STUDIES**Formulation of compound 1:**

- For oral (*p.o.*) administration: to the desired quantity (0.5-15 mg) of the compound given above as 'Compound 1' in a glass tube, some glass beads were added and the substance was milled by vortexing for 2 minutes. After addition of 1 ml of a solution of 1% methylcellulose in water, the compound was suspended by vortexing for 10 minutes. For concentrations up and above 1 mg/ml remaining particles in the suspension were further suspended by using an ultrasonic bath.

10 EXAMPLE 3: PHARMACOLOGICAL TEST RESULTS

Cannabinoid receptor affinity and functional *in vitro* data data obtained according to the protocols given above are shown in the table below.

15 Table 1: pharmacological data

Compound nr	Human cannabinoid-CB ₁ receptor	
	<i>In vitro</i> affinity pK _i value	<i>In vitro</i> antagonism pA ₂ -value (arachidonic acid release)
Compound 1	7.7	-
Compound 2	7.0	-
Compound 4	7.0	7.7
Compound 8	6.8	-